UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 09/864,364 | 05/25/2001 | Saburo Sone | 04853.0071 | 1599 |

22852 7590 10/23/2002

FINNEGAN, HENDERSON, FARABOW, GARRETT &
DUNNER LLP
1300 I STREET, NW
WASHINGTON, DC 20006

| EXAMINER |
|---|
| LI, QIAN J |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1632 | 12 |

DATE MAILED: 10/23/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. 09/864,364 | Applicant(s) SONE ET AL. | |
|---|---|---|---|
| | Examiner Q. Janice Li | Art Unit 1632 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Peri d for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *15 July 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-5,7,9-19 and 21-25* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,7,9-19 and 21-25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

## DETAILED ACTION

The amendment filed on July 15, 2002 has been entered and assigned as Paper #11. The Examiner assigned to examine your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to examiner Q. Janice Li, at Group Art Unit 1632. Claims 6, 8, and 20 have been canceled. Claims 1-5, 7, 9, 10, 13-16, 24, and 25 have been amended. Currently, claims 1-5, 7, 9-19, and 21-25 are pending and under examination.

Unless otherwise indicated, previous rejections that have been rendered moot in view of the amendment to pending claims will not be reiterated.

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 25 stands rejected and claims 18 and 24 is newly rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 18 is vague and indefinite because of the claim recitation "mouse antibody". It is unclear the phrase embraces an antibody against a mouse antigen or an antibody made in the mouse, thus, the metes and bounds of the claim is unclear.

Claims 24 and 25 are vague and indefinite because it is incomplete. The claims provide for evaluating efficiencies of treatment or for determining the effect of a test substance on bone metastasis, however, there is no step or conclusion to indicate how the efficiency of the treatment or the effect of the test substance is determined, which would clearly relates back to the preamble. Method claims need not recite all operating details but should at least recite positive, active steps so that the claims will set out and circumscribe a particular area with a reasonable degree of precision and particularity and make clear what subject matter that claims encompass as well as make clear the subject matter from which others would be precluded, *Ex parte Erlich*, 3 USPQ2d 1011 at 6.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-5, 7, 10-19, 21, 24, and 25 stand rejected and claims 9, 22, 23 are newly rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for producing a rodent bone metastasis model animal by intravenous administration of human lung small cell carcinoma cell line SBC-5 cells, wherein the rodent is immunodeficient SCID mouse depleted of CD8+ T cells, does not reasonably provide enablement for producing any rodent bone metastasis model animal by *any* peripheral administration of *any* cancer or tumor cells in *any* immunodeficient rodents. The specification does not enable any person skilled in the art to which it pertains, or

with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

As discussed in detail in the Office action paper #8, the specification teaches that out of eight different types of human lung cancer cell lines, only one SBC-5 developed metastatic colonies in bone and other organs. Thus, the applicant was not successful in creating such a metastatic model with any human lung cancer cells, let alone other cancer cell types. In view of the state of the art and the levels of the skilled in the art, *Fodstad et al* (J Cell Biochem 1994;56:23-28) teach, "IMMUNODEFICIENT NUDE AND SCID MICE, AS WELL AS NUDE RATS, PROVIDE IMPORTANT TOOLS FOR TUMOR BIOLOGY RESEARCH. ONE MAJOR DRAWBACK HAS BEEN THE VERY LOW FREQUENCY OF SPONTANEOUS METASTASIS OBSERVED WHEN HUMAN TUMORS ARE GROWN SUBCUTANEOUSLY IN SUCH RODENTS", "THE HEALTH STATUS OF THE ANIMALS, THE NATURE OF THEIR IMMUNODEFICIENCY, THE PREPARATION OF TUMOR MATERIAL, AND THE SITE OR ROUTE OF CELL ADMINISTRATION SEEM TO HAVE A STRONG IMPACT ON BOTH THE DEVELOPMENT OF METASTATIC TUMOR LESIONS AND ON THE PATTERN OF METASTASIS" (right column, page 23). This has proven to be true in other experimental models. For example, *Engebraaten et al* (Int J Cancer 1999;82:219-25) teach that two lines of breast cancer cells, MT-1 and MA-11, produced different pattern of tumor metastasis in a nude rat model, wherein MT-1 but not MA-11 leads to bone/bone marrow metastasis by intracardial injection (section bridging left and right columns, page 221), whereas intravenous injection of MT-1 only lead to pulmonary, but not bone metastasis (left column page 222).

In paper #10, applicants argue that the specification teaches that the PTHrP highly expressed cell is crucial in the formation of bone metastasis and hypercalcemia.

However, claim 1 embraces a broad range of cancer cells, not limited to human lung or breast cancer highly expressing PTHrP.

For reasons of record and set forth foregoing, the instant specification fails to meet the statutory enablement requirement set forth under 35 U.S.C. §112, 1st paragraph.

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 3-10, 12, and 19-25 stand rejected under 35 U.S.C. 102(b) as being anticipated by *Namikawa et al* (US 5,643,551).

Applicants argue in paper #10 that the method of *Namikawa et al* requires the prior introduction of viable human tissue which can thereafter be colonized with human metastatic cells, whereas the claimed invention exhibits metastasis of injected tumor cells in the animal's own bone tissue.

The argument has been carefully considered but found not persuasive. This is because the claims only require that the rodent animal is immundeficient, the limitation of colonization in its own bone tissue is not present in the claims. Therefore, *Namikawa et al* teach all the elements of the claims, and the rejection stands.

Claims 1-5, 7, 9-19, and 21-25 are newly rejected under 35 U.S.C. 102(b) as being clearly anticipated by *Miki et al* ((Oncol Res 2000 12(5):209-17)).

*Miki et al* teach establishing an NK-cell depleted SCID mice model for bone and multi-organ metastases using human lung small cell carcinoma SBC5 cells by intravenous injection (abstract), wherein the NK-cell depletion was conducted by anti-mouse IL-2 receptor beta-chain antibody (last paragraph, page 209), wherein the SBC5 cells express PTHrP highly (tab. 5). *Miki et al* teach that the model is useful for developing therapeutic modalities for lung cancer patients with bone metastases (last paragraph, page 215). Thus, *Miki et al* anticipate the instant claims.

Claims 1, 2, 4, 5, 10, 11, 24, and 25 are newly rejected under 35 U.S.C. 102(b) as being anticipated by *Engebraaten et al* (Int J Cancer 1999;82:219-25).

*Engebraaten et al* teach establishing a nude rat model for bone metastasis using human breast cancer cells MT-1 by intracardial injection, which exhibited consistent bone/bone marrow metastases in addition to brain and spinal cord tumors. *Engebraaten et al* go on to teach that the model is a valuable tool for studying mechanisms of metastasis and for preclinical testing of anti-metastatic therapy regimens. Thus, *Engebraaten et al* anticipate the instant claims.

Please note that claim recitation, "highly expressing PTHrP" has not been given patentable weight in determining the novelty of the invention in this rejection. This is because it merely states an intrinsic property of the cells derived from human lung cancer or breast cancer" and the Office does not have the facilities for examining and comparing applicant's product with the product of the prior art in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is upon the applicant to prove that the prior art products do not necessarily or

inherently possess characteristics of claimed product, which requires factual evidence demonstrating that actual, unobvious differences exist and to establish patentable differences. See Ex parte Phillips, 28 USPQ 1302, 1303 (BPBI 1993), In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ2d 1922, 1923 (BPAI 1989).

Claims 1, 4, 5, 7, 9, 10, 13-15, and 21-25 are newly rejected under 35 U.S.C. 102(e) as being clearly anticipated by *Sawyers et al* (US 6,365,797).

*Sawyers et al* teach establishing a SCID mouse model for bone metastasis using human prostate cancer LAPC-4 cells by subcutaneous injection, which exhibited consistent bone/bone marrow metastases in addition to lymph and pulmonary metastasis tumors, wherein an enhanced frequency of bone metastasis was observed in a subset of the mice pretreated with a combination of radiation and NK cell depletion (column 24, lines 31-35). *Sawyers et al* teach that the model provides assays for determining the effect of candidate therapeutic compositions or treatments on the growth of prostate cancer cells (column 8, lines 21-41). Thus, *Sawyer et al* anticipate the instant claims.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 2, 11, 13-18 stand rejected under 35 U.S.C. 103(a) as being unpatentable over *Namikawa et al* (US 5,643,551), in view of *Yano et al* (Intl J Cancer 1996;67:211-17) and *Mundy et al* (Seminars in Oncol 2001 Apr;28:35-44).

In paper #10, applicants argue that Yano fails to obtain any bone metastases, and Mundy fails to demonstrate that peripheral injection of tumor cells results in bone metastasis, that there is no motivation to combine.

In response, the Yano reference is relied upon for NK cell depletion, and the Mundy reference is relied upon for teachings of PTHrP expressing breast cancer cells. The motivation to combine is also clearly stated in Paper #9. Further, it is noted that the test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference; nor is it that the claimed invention must be expressly suggested in any one or all of the references. Rather, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981).

For reasons of record and those set forth above, the rejection stands.

Claims 10, and 16-18 are newly rejected under 35 U.S.C. 103(a) as being unpatentable over *Sawyers et al* (US 6,365,797), and in view of *Yano et al* (Intl J Cancer 1996;67:211-17).

Claims 16-18 are further drawn to depleting NK cells with a monoclonal anti-IL-2 receptor beta-chain antibody. *Sawyers et al* teach establishing a SCID mouse model for bone metastasis using human prostate cancer LAPC-4 cells by subcutaneous injection, which exhibited consistent bone/bone marrow metastases in addition to lymph and pulmonary metastasis tumors, wherein an enhanced frequency of bone metastasis was observed in a subset of the mice pretreated with a combination of radiation and NK cell depletion (column 24, lines 31-35). *Sawyers et al* do not particularly teach how the NK-depletion was achieved. However, Yano et al teach that pre-treatment with anti-mouse IL-2 receptor beta chain antibody would deplete CD8+ T cells and enhance tumor metastasis in a SCID mouse tumor model.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to employ the antibody taught by *Yano et al* in the methods of *Sawyers et al,* for NK cell depletion with a reasonable expectation of success. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Q. Janice Li whose telephone number is 703-308-7942. The examiner can normally be reached on 8:30 am - 5 p.m., Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah J. Reynolds can be reached on 703-305-4051. The fax numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of formal matters can be directed to the patent analyst, Dianiece Jacobs, whose telephone number is (703) 305-3388.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1235. The faxing of such papers must conform to the notice published in the Official Gazette 1096 OG 30 (November 15, 1989).

Q. Janice Li
Examiner
Art Unit 1632

QJL
October 10, 2002

ANNE M. WEHBE' PH.D
PRIMARY EXAMINER